THE IMPORTANCE OF PHYSIOLOGICAL ASSAY IN THE STANDARDIZATION OF SOME DRUGS.

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THE main factors which have been responsible for the increasing interest and change of attitude shown in problems connected with the use of drugs in the treatment of disease, and especially in their standardization, are mainly these: The first was the appearance of the new Pharmacopœia, causing as it did many discussions in regard to the admission of new remedies and a change in the standard of some of the older preparations. The second was the establishing of the Council on Pharmacy and Chemistry, which exposed false claims of many "quack" remedies by showing that they were entirely without value as remedies for the ailments for which they were so highly recommended. This council also investigated the condition of many official preparations, and showed that many of them were far from being up to standard. The third factor, and by far the most important, was the establishing of drug laboratories for the state and national pure food and drugs law. These laboratories have submitted to them for analysis every known form of remedies for the treatment of disease. Very frequently chemists are unable to give conclusive information about certain remedies because of the lack of the necessary equipment for physiological examinations.

The uniformity in strength of any drug is one of the first essentials. Its preparation shall also possess physiological qualities to a uniform degree—in other words, should be of a uniform standard.

The recent Pharmacopœia has made greater advances in standardization than any previous one, in that it requires in many more instances than formerly that the drug shall be standardized so as to contain a certain fixed percentage of its active principle, thus assuring the physician a more definite and reliable preparation.

Probably the foremost cause of the variation of standards is the fact that the drugs often vary notoriously in content of active principle. This variation depends upon climatic conditions, different localities, the time of year when drug is collected, and, probably of greatest importance, upon the manner in which the drug is prepared for market and the way it is preserved before it is used. This, then, accounts for the varying degree of physiological activity

of preparations made exactly in the same percentage of crude drugs, but using drugs from different sources.

No insistence is needed on the desirability of a uniform standard of activity for all drugs, and especially such as contain especially highly active principles of highly toxic nature. In the case of some, such as cinchona, hydrastis, opium or nux vomica, such a standardization is easily carried out by chemical means. These drugs owe their activity to the presence of certain specific alkaloids which are of such a basic nature that they unite readily with acids, thus affording a means of assay. These particular alkaloids are also sufficiently stable that they can withstand the action of strong acids, alkalies, and quite a high heat, and can be determined gravimetrically.

There are, however, other drugs in which the active principle is of such a nature that attempts at chemical investigation, if not misleading, are unsatisfactory, even though the active principles are recognized and something is known of their chemical nature. Typical instances of such drugs are digitalis, strophanthus, squills, ergot, cannabis indica, aconite, and others. The active principles of the first three, called the "cardiac group," are of a glucosidal nature, and as yet there have been no good chemical methods given by which these principles can be isolated quantitatively. However, a very good and simple physiological method has been in use for years and is used by all well-equipped manufacturing houses at the present time. Until very recently it was not known that ergot contained its active principle in the form of an alkaloid, and heretofore it has been analyzed physiologically by its effect upon the rooster's comb. Although the alkaloidal ergotoxin exists in ergot, it is present in such very small quantities that it would be difficult to isolate it quantitatively.

Cannabis indica, a notoriously variable drug, is highly active, but unfortunately its chemistry has not been sufficiently investigated, so that there is a consensus of opinion among authorities as to what its active principle is. However, the drug can be thoroughly standardized by observing the nervous symptoms produced by a given dose in a dog or cat.

Physicians and pharmacists alike have recognized the necessity of some way of standardizing these preparations, and have introduced physiological methods of assay which are being used by all of the larger manufacturing houses, and it is mainly due to these that methods are being perfected.

That these drugs and their preparations vary has been proven by the foremost pharmacologists.

Dixon, in the *British Medical Journal*, says that he and Haynes demonstrated in Cambridge the variability of action of the group of cardiac tonics, including digitalis, strophanthus and squills. He makes the statement that he believes hundreds of patients die annually from digitalis and its allies in not possessing the exact quantity of active principle required of them.

Houghton states, in the *Journal* of the Medical Association, that he found by testing preparations of the well-known active drug strophanthus that some were three times as strong as others.

A series of investigations by Edmunds on tincture of digitalis is very interesting, and shows very plainly the uncertainty of this particular preparation. His object in collecting the samples was to get the greatest variety in respect to different methods of manufacture, drugs from different sources, and tinctures made from supposedly assayed fluid extracts from certain manufacturing houses. His results showed that some of the tinctures are almost four times as strong as others, or, in other words, that four or five drops of one will produce the same effect as fifteen of another preparation. Since the average dose of tincture of aconite is ten drops, it can be plainly seen what a marked variation in activity there would exist if these were dispensed. Another interesting feature shown by this investigation was that a pharmacist made two preparations, one being four times stronger than the other. Four samples for the same wholesale house varied very markedly, but this was not strange, since they made no pretense at physiological assay.

These instances I have mentioned are by no means rare. They exist in every drug and its preparations for which there is no chemical method of assay, and it is merely a question of "luck" with the patient when he gets his prescription, and unless very rapid advances are made to perfect and simplify methods for physiological assay for these questionable drugs this dangerous condition will become worse instead of better.

I trust that you will not infer from the above that I am pessimistic in regard to this precarious condition of certain official preparations on the market. During a period of nearly two years we have come in contact with nearly all druggists of this state by analyzing one or more of their own prepared official preparations. The condition in which we found some of the more simple ones leaves no room for doubt that they would make a decided failure in the attempt to manufacture these more difficult preparations. At

present our drug laboratory is amply equipped for chemical investigation, but the very necessary equipment for physiological assay is still wanting. Until we do have this installed we are helpless to give conclusive information in regard to the relative values of the drugs I have mentioned, and many others.

THE MANUFACTURE OF ENAMELED WARE.

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THE manufacture of enameled-steel cooking utensils is an industry which could and should be carried on in Kansas. Her natural resources (especially her minerals and abundant supply of fuel), her industries allied to enamel making, and her central location, are all points in favor of Kansas as compared with other states for the location of enameling works.

An enamel is a vitreous silicate resembling glass or porcelain, but which forms an intimate coating on the surface of a metal. On a vessel which is to be used for cooking the enamel must not be brittle and must have a coefficient of expansion near that of the metal. It must resist both acids and alkalies and must contain no lead or other poisonous materials.

The following materials are used in the making of enamel for cooking utensils: Flint, quartz and glass-sand supply the silica, feldspar and clay the alumina. Fluorspar and cryolite are added on account of their fluorin content and assist in making the enamel opaque, thus giving it "body." Soda-ash and pearl-ash are fluxes, and borax, which acts as a flux also, keeps the enamel from being brittle and brings out the color from the metallic oxids used as pigments. Saltpeter and Chili saltpeter act as decolorizers, as well as being fluxes; and magnesium sulfate and ammonium carbonate, which are added to thicken the wet enamel, are among the raw materials, as well as carbon, chromium oxid, cobalt oxid, copper oxid, uranium oxid, selenium and gold oxid, and especially tin oxid, antimony oxid and zinc oxid, which are pigments giving color to the enamel.

Enameling is still held as a secret art, and the formulas are carefully guarded. In the company with which I was chemist for three years very few visitors are allowed to go through the works, and none of these are taken through the laboratory or the room in which the enamels are mixed. Each of the raw materials used has a number, and they are always designated as such. They are shipped so that the bill of lading contains only the number. All